```
                                                             GGCACGAGTCGGAGCCGGG

CGGAGGGGAGGGGGGAAAGAGGAGCGCAGGGTGAGAGTGAGCCGCAGGCTTCGGGAGGCGAGGGGGCGGGGGGAGCAGC

                                                              M   P   G   E     4
GCCGAGGYCGCCGCCTCCGCCTCCGCGCCTAGGACTAGGGGGTGGGGGACGGACAAGCCCCCG ATG CCG GGG GAG    12

 T   E   E   P   R   P   P   E   Q   Q   D   Q   E   G   G   E   A   A   K   A     24
ACG GAA GAG CCG AGA CCC CCG GAG CAG CAG GAC CAG GAA GGG GGA GAG GCG GCC AAG GCG    72

 A   P   E   E   P   Q   Q   R   P   P   E   A   V   A   A   A   P   A   G   T     44
GCT CCG GAG GAG CCC CAA CAA CGG CCC CCT GAG GCG GTC GCG GCG GCG CCT GCA GGG ACC   132

 T   S   S   R   V   L   R   G   G   R   D   R   G   R   A   A   A   A   A   A     64
ACT AGC AGC CGC GTG CTG AGG GGA GGT CGG GAC CGA GGC CGG GCC GCT GCG GCC GCC GCC   192

 A   A   A   V   S   R   R   R   K   A   E   Y   P   R   R   R   R   S   S   P     84
GCC GCA GCT GTG TCC CGC CGG AGG AAG GCC GAG TAT CCC CGC CGG CGG AGG AGC AGC CCC   252

 S   A   R   P   P   D   V   P   G   Q   Q   P   Q   A   A   K   S   P   S   P    104
AGC GCC AGG CCT CCC GAC GTC CCC GGG CAG CAG CCC CAG GCC GCG AAG TCC CCG TCT CCA   312

 V   Q   G   K   K   S   P   R   L   L   C   I   E   K   V   T   T   D   K   D    124
GTT CAG GGC AAG AAG AGT CCG CGA CTC CTA TGC ATA GAA AAA GTA ACA ACT GAT AAA GAT   372

 P   K   E   E   K   E   E   E   D   D   S   A   L   P   Q   E   V   S   I   A    144
CCC AAG GAA GAA AAA GAG GAA GAA GAC GAT TCT GCC CTC CCT CAG GAA GTT TCC ATT GCT   432
```

FIG.1A

```
 A   S   R   P   S   R   G   W   R   S   S   R   T   S   V   S   R   H   R   D   164
GCA TCT AGA CCT AGC CGG GGC TGG CGT AGT AGT AGG ACA TCT GTT TCT CGC CAT CGT GAT   492

 T   E   N   T   R   S   S   R   S   K   T   G   S   L   Q   L   I   C   K   S   184
ACA GAG AAC ACC CGA AGC TCT CGG TCC AAG ACC GGT TCA TTG CAG CTC ATT TGC AAG TCA   552

 E   P   N   T   D   Q   L   D   Y   D   V   G   E   E   H   Q   S   P   G   G   204
GAA CCA AAT ACA GAC CAA CTT GAT TAT GAT GTT GGA GAA GAG CAT CAG TCT CCA GGT GGC   612

 I   S   G   E   E   E   E   E   E   E   E   E   M   L   I   S   E   E   E   I   224
ATT AGT GGT GAA GAG GAA GAG GAG GAG GAA GAA GAG ATG TTA ATC AGT GAA GAG GAG ATA   672

 P   F   K   D   D   P   R   D   E   T   Y   K   P   H   L   E   R   E   T   P   244
CCA TTC AAA GAT GAT CCA AGA GAT GAG ACC TAC AAA CCC CAC TTA GAA AGG GAA ACC CCA   732

 K   P   R   R   K   S   G   K   V   K   E   E   K   E   K   K   E   I   K   V   264
AAG CCA CGG AGA AAA TCA GGG AAG GTA AAA GAA GAG AAG GAG AAG AAG GAA ATT AAA GTG   792

 E   V   E   V   E   V   K   E   E   E   N   E   I   R   E   D   E   E   P   P   284
GAA GTA GAG GTG GAG GTG AAA GAA GAG GAG AAT GAA ATT AGA GAG GAT GAG GAA CCT CCA   852

 R   K   R   G   R   R   R   K   D   D   K   S   P   R   L   P   K   R   R   K   304
AGG AAG AGA GGA AGA AGA CGA AAA GAT GAC AAA AGT CCA CGT TTA CCC AAA AGG AGA AAA   912

 K   P   P   I   Q   Y   V   R   C   E   M   E   G   C   G   T   V   L   A   H   324
AAG CCT CCA ATC CAG TAT GTC CGT TGT GAG ATG GAA GGA TGT GGA ACT GTC CTT GCC CAT   972
```

FIG.1B

```
 P  R  Y  L  Q  H  H  I  K  Y  Q  H  L  L  K  K  K  Y  V  C   344
CCT CGC TAT TTG CAG CAC CAC ATT AAA TAC CAG CAT TTG CTG AAG AAG AAA TAT GTA TGT  1032

 P  H  P  S  C  G  R  L  F  R  L  Q  K  Q  L  L  R  H  A  K   364
CCC CAT CCC TCC TGT GGA CGA CTC TTC AGG CTT CAG AAG CAA CTT CTG CGA CAT GCC AAA  1092

 H  H  T  D  Q  R  D  Y  I  C  E  Y  C  A  R  A  F  K  S  S   384
CAT CAT ACA GAT CAA AGG GAT TAT ATC TGT GAA TAT TGT GCT CGG GCC TTC AAG AGT TCC  1152

 H  N  L  A  V  H  R  M  I  H  T  G  E  K  P  L  Q  C  E  I   404
CAC AAT CTG GCA GTG CAC CGG ATG ATT CAC ACT GGC GAG AAG CCA TTA CAA TGT GAG ATC  1212

 C  G  F  T  C  R  Q  K  A  S  L  N  W  H  M  K  K  H  D  A   424
TGT GGA TTT ACT TGT CGA CAA AAG GCA TCT CTT AAT TGG CAC ATG AAG AAA CAT GAT GCA  1272

 D  S  F  Y  Q  F  S  C  N  I  C  G  K  K  F  E  K  K  D  S   444
GAC TCC TTC TAC CAG TTT TCT TGC AAT ATC TGT GGC AAA AAA TTT GAG AAG AAG GAC AGC  1332

 V  V  A  H  K  A  K  S  H  P  E  V  L  I  A  E  A  L  A  A   464
GTA GTG GCA CAC AAG GCA AAA AGC CAC CCT GAG GTG CTG ATT GCA GAA GCT CTG GCT GCC  1392

 N  A  G  A  L  I  T  S  T  D  I  L  G  T  N  P  E  S  L  T   484
AAT GCA GGC GCC CTC ATC ACC AGC ACA GAT ATC TTG GGC ACT AAC CCA GAG TCC CTG ACG  1452

 Q  P  S  D  G  Q  G  L  P  L  L  P  E  P  L  G  N  S  T  S   504
CAG CCT TCA GAT GGT CAG GGT CTT CCT CTT CTT CCT GAG CCC TTG GGA AAC TCA ACC TCT  1512
```

FIG.1C

```
 G   E   C   L   L   L   E   A   E   G   M   S   K   S   Y   C   S   G   T   E    524
GGA GAG TGC CTA CTG TTA GAA GCT GAA GGG ATG TCA AAG TCA TAC TGC AGT GGG ACG GAA  1572

 R   V   S   L   M   A   D   G   K   I   F   V   G   S   G   S   S   G   G   T    544
CGG GTG AGC CTG ATG GCT GAT GGG AAG ATC TTT GTG GGA AGC GGC AGC AGT GGA GGC ACT  1632

 E   G   L   V   M   N   S   D   I   L   G   A   T   T   E   V   L   I   E   D    564
GAA GGG CTG GTT ATG AAC TCA GAT ATA CTC GGT GCT ACC ACA GAG GTT CTG ATT GAA GAT  1692

 S   D   S   A   G   P   *                                                       570
TCA GAC TCT GCC GGA CCT TAG TGGACAGGAAGACTTGGGGCATGGGACAGCTCAGACTTTGTATTTAAAAGT  1761

TAAAAAGGACAAAAAAAAAAAAAAAAA                                                    1791
```

FIG.1D

```
                    GCACGAGCGGAGAGCCGCGCAGGGCGCGGGCCGCGCGGGGTGGGGCAGCCGGAGCGCA

GGCCCCCGATCCCCGGCGGGCGCCCCCGGGCCCCCGCGCGCGCCCCGGCCTCCGGGAGACTGGCGCATGCCACGGAGCG

CCCCTCGGGCCGCCGCCGCTCCTGCCCGGGCCCCTGCTGCTGCTGCTGTCGCCTGCGCCTGCTGCCCCAACTCGGCGCC

                                                                         M   F      2
CGACTCACAAAGAAACATCATGTTCGCTCCTTAGCAGGCAAACGACTTTTCTCCTCGCCTCCTCGCCCCGC ATG TTC      6

 R   T   K   R   S   A   L   V   R   R   L   W   R   S   R   A   P   G   G   E     22
AGG ACC AAA CGA TCT GCG CTC GTC CGG CGT CTC TGG AGG AGC CGT GCG CCC GGC GGC GAG    66

 D   E   E   E   G   A   G   G   G   G   G   G   G   E   L   R   G   E   G   A     42
GAC GAG GAG GAG GGC GCA GGG GGA GGT GGA GGA GGA GGC GAG CTG CGG GGA GAA GGG GCG   126

 T   D   S   R   A   H   G   A   G   G   G   G   P   G   R   A   G   C   C   L     62
ACG GAC AGC CGA GCG CAT GGG GCC GGT GGC GGC GGC CCG GGC AGG GCT GGA TGC TGC CTG   186

 G   K   A   V   R   G   A   K   G   H   H   H   P   H   P   P   A   A   G   A     82
GGC AAG GCG GTG CGA GGT GCC AAA GGT CAC CAC CAT CCC CAC CCG CCA GCC GCG GGC GCC   246

 G   A   A   G   G   A   E   A   D   L   K   A   L   T   H   S   V   L   K   K    102
GGC GCG GCC GGG GGC GCC GAG GCG GAT CTG AAG GCG CTC ACG CAC TCG GTG CTC AAG AAA   306

 L   K   E   R   Q   L   E   L   L   L   Q   A   V   E   S   R   G   G   T   R    122
CTG AAG GAG CGG CAG CTG GAG CTG CTG CTC CAG GCC GTG GAG TCC CGC GGC GGG ACG CGC   366
```

FIG.2A

```
 T   A   C   L   L   L   P   G   R   L   D   C   R   L   G   P   G   A   P   A    142
ACC GCG TGC CTC CTG CTG CCC GGC CGC CTG GAC TGC AGG CTG GGC CCG GGG GCG CCC GCC   426

 G   A   Q   P   A   Q   P   P   S   S   Y   S   L   P   L   L   L   C   K   V    162
GGC GCG CAG CCT GCG CAG CCG CCC TCG TCC TAC TCG CTC CCC CTC CTG CTG TGC AAA GTG   486

 F   R   W   P   D   L   R   H   S   S   E   V   K   R   L   C   C   C   E   S    182
TTC AGG TGG CCG GAT CTC AGG CAT TCC TCG GAA GTC AAG AGG CTG TGT TGC TGT GAA TCT   546

 Y   G   K   I   N   P   E   L   V   C   C   N   P   H   H   L   S   R   L   C    202
TAC GGG AAG ATC AAC CCC GAG CTG GTG TGC TGC AAC CCC CAT CAC CTT AGC CGA CTC TGC   606

 E   L   E   S   P   P   P   P   Y   S   R   Y   P   M   D   F   L   K   P   T    222
GAA CTA GAG TCT CCC CCC CCT CCT TAC TCC AGA TAC CCG ATG GAT TTT CTC AAA CCA ACT   666

 A   D   C   P   D   A   V   P   S   S   A   E   T   G   G   T   N   Y   L   A    242
GCA GAC TGT CCA GAT GCT GTG CCT TCC TCC GCT GAA ACA GGG GGA ACG AAT TAT CTG GCC   726

 P   G   G   L   S   D   S   Q   L   L   L   E   P   G   D   R   S   H   W   C    262
CCT GGG GGG CTT TCA GAT TCC CAA CTT CTT CTG GAG CCT GGG GAT CGG TCA CAC TGG TGC   786

 V   V   A   Y   W   E   E   K   T   R   V   G   R   L   Y   C   V   Q   E   P    282
GTG GTG GCA TAC TGG GAG GAG AAG ACG AGA GTG GGG AGG CTC TAC TGT GTC CAG GAG CCC   846

 S   L   D   I   F   Y   D   L   P   Q   G   N   G   F   C   L   G   Q   L   N    302
TCT CTG GAT ATC TTC TAT GAT CTA CCT CAG GGG AAT GGC TTT TGC CTC GGA CAG CTC AAT   906
```

FIG.2B

```
 S   D   N   K   S   Q   L   V   Q   K   V   R   S   K   I   G   C   G   I   Q     322
TCG GAC AAC AAG AGT CAG CTG GTG CAG AAG GTG CGG AGC AAA ATC GGC TGC GGC ATC CAG     966

 L   T   R   E   V   D   G   V   W   V   Y   N   R   S   S   Y   P   I   F   I     342
CTG ACG CGG GAG GTG GAT GGT GTG TGG GTG TAC AAC CGC AGC AGT TAC CCC ATC TTC ATC    1026

 K   S   A   T   L   D   N   P   D   S   R   T   L   L   V   H   K   V   F   P     362
AAG TCC GCC ACA CTG GAC AAC CCT GAC TCC AGG ACG CTG TTG GTA CAC AAG GTG TTC CCC    1086

 G   F   S   I   K   A   F   D   Y   E   K   A   Y   S   L   Q   R   P   N   D     382
GGT TTC TCC ATC AAG GCT TTC GAC TAC GAG AAG GCG TAC AGC CTG CAG CGG CCC AAT GAC    1146

 H   E   F   M   Q   Q   P   W   T   G   F   T   V   Q   I   S   F   V   K   G     402
CAC GAG TTT ATG CAG CAG CCG TGG ACG GGC TTT ACC GTG CAG ATC AGC TTT GTG AAG GGC    1206

 W   G   Q   C   Y   T   R   Q   F   I   S   S   C   P   C   W   L   E   V   I     422
TGG GGT CAG TGC TAC ACC CGC CAG TTC ATC AGC AGC TGC CCG TGC TGG CTA GAG GTC ATC    1266

 F   N   S   R   *                                                               426
TTC AAC AGC CGG TAG  CCGCGTGCGGAGGGGACAGAGCGTGAGCTGAGCAGGCCACACTTCAAACTACTTTGCT    1278

GCTAATATTTTCCTCCTGAGTGCTTGCTTTTCATGCAAACTCTTTGGTCTTTTTTTTTTTGTTTGTTGGTTGGTTTTCT

TCTTCTCGTCCTCGTTTGTGTTCTGTTTTGTTTCGCTCTTTGAGAAATAGCTTATGAAAAGAATTGTTGGGGGTTTTTT

TGGAAGAAGGGGCAGGTATGATCGGCAGGACACCCTGATAGGAAGAGGGGAAGCAGAAATCCAAGCACCACCAAACACA
```

FIG.2C

GTGTATGAAGGGGGGCGGTCATCATTTCACTTGTCAGGAGTGTGTGTGAGTGTGAGTGTGCGGCTGTGTGTGCACGCGT

GTGCAGGAGCGGCAGATGGGGAGACAACGTGCTCTTTGTTTTGTGTCTCTTATGGATGTCCCCAGCAGAGAGGTTTGCA

GTCCCAAGCGGTGTCTCTCCTGCCCCTTGGACACGCTCAGTGGGGCAGAGGCAGTACCTGGGCAAGCTGGCGGCTGGGG

TCCCAGCAGCTGCCAGGAGCACGGCTCTGTCCCCAGCCTGGGAAAGCCCCTGCCCCTCCTCTCCCTCATCAAGGACACG

GGCCTGTCCACAGGCTTCTGAGCAGCGAGCCTGCTAGTGGCCGAACCAGAACCAATTATTTTCATCCTTGTCTTATTCC

CTTCCTGCCAGCCCCTGCCATTGTAGCGTCTTTCTTTTTTGGCCATCTGCTCCTGGATCTCCCTGAGATGGGCTTCCCA

AGGGCTGCCGGGGCAGCCCCCTCACAGTATTGCTCACCCAGTGCCCTCTCCCCTCAGCCTCTCCCCTGCCTGCCCTGGT

GACATCAGGTTTTTCCCGGACTTAGAAAACCAGCTCAGCACTGCCTGCTCCCATCCTGTGTGTTAAGCTCTGCTATTAG

GCCAGCAAGCGGGGATGTCCCTGGGAGGGACATGCTTAGCAGTCCCCTTCCCTCCAAGAAGGATTTGGTCCGTCATAAC

CCAAGGTACCATCCTAGGCTGACACCTAACTCTTCTTTCATTTCTTCTACAACTCATACACTCGTATGATACTTCGACA

CTGTTCTTAGCTCAATGAGCATGTTTAGACTTTAACATAAGCTATTTTTCTAACTACAAAGGTTTAAATGAACAAGAGA

AGCATTCTCATTGGAAATTTAGCATTGTAGTGCTTTGAGAGAGAAAGGACTCCTGAAAAAAAAACCTGAGATTTATTAAA

GAAAAAAATGTATTTTATGTTATATATAAATATATTATTACTTGTAAATATAAAGACGTTTTATAAGCATCATTATTTA

FIG.2D

TGTATTGTGCAATGTGTATAAACAAGAAAAATAAAGAAAAGATGCACTTTGCTTTAATATAAATGCAAATAACAAATGC

CAAATTAAAAAAGATAAACACAAGATTGGTGTTTTTTCCTATGGGTGTTATCACCTAGCTGAATGTTTTTCTAAAGGAG

TTTATGTTCCATTAAACGATTTTTAAAATGTACACTTGAAAAAAAAAAAAAAAAA

FIG.2E

```
                                                                GGCACGAGGTTGCCCTGGCGGAGCAGAGACAGGCCCTCGGGGTGGAGGTC

                                                          M  C  N  T  P  T  Y  C  D  L      10
TTTGGTTTCATAAGAGCCTGAGAGAGATTTTTCTAAGAT ATG TGT AAC ACA CCA ACG TAC TGT GAC CTA      30

 G  K  A  A  K  D  V  F  N  K  G  Y  G  F  G  M  V  K  I  D      30
GGA AAG GCT GCT AAG GAT GTC TTC AAC AAA GGA TAT GGC TTT GGC ATG GTC AAG ATA GAC      90

 L  K  T  K  S  C  S  G  V  E  F  S  T  S  G  H  A  Y  T  D      50
CTG AAA ACC AAG TCT TGT AGT GGA GTG GAA TTT TCT ACT TCT GGT CAT GCT TAC ACT GAT     150

 T  G  K  A  S  G  N  L  E  T  K  Y  K  V  C  N  Y  G  L  T      70
ACA GGG AAA GCA TCA GGC AAC CTA GAA ACC AAA TAT AAG GTC TGT AAC TAT GGA CTT ACC     210

 F  T  Q  K  W  N  T  D  N  T  L  G  T  E  I  S  W  E  N  K      90
TTC ACC CAG AAA TGG AAC ACA GAC AAT ACT CTA GGG ACA GAA ATC TCT TGG GAG AAT AAG     270

 L  A  E  G  L  K  L  T  L  D  T  I  F  V  P  N  T  G  K  K     110
TTG GCT GAA GGG TTG AAA CTG ACT CTT GAT ACC ATA TTT GTA CCG AAC ACA GGA AAG AAG     330

 S  G  K  L  K  A  S  Y  K  R  D  C  F  S  V  G  S  N  V  D     130
AGT GGG AAA TTG AAG GCC TCC TAT AAA CGG GAT TGT TTT AGT GTT GGC AGT AAT GTT GAT     390

 I  D  F  S  G  P  T  I  Y  G  W  A  V  L  A  F  E  G  W  L     150
ATA GAT TTT TCT GGA CCA ACC ATC TAT GGC TGG GCT GTG TTG GCC TTC GAA GGG TGG CTT     450
```

FIG.3A

```
 A   G   Y   Q   M   S   F   D   T   A   K   S   K   L   S   Q   N   N   F   A    170
GCT GGC TAT CAG ATG AGT TTT GAC ACA GCC AAA TCC AAA CTG TCA CAG AAT AAT TTC GCC    510

 L   G   Y   K   A   A   D   F   Q   L   H   T   H   V   N   D   G   T   E   F    190
CTG GGT TAC AAG GCT GCG GAC TTC CAG CTG CAC ACA CAT GTG AAC GAT GGC ACT GAA TTT    570

 G   G   S   I   Y   Q   K   V   N   E   K   I   E   T   S   I   N   L   A   W    210
GGA GGT TCT ATC TAC CAG AAG GTG AAT GAG AAG ATT GAA ACA TCC ATA AAC CTT GCT TGG    630

 T   A   G   S   N   N   T   R   F   G   I   A   A   K   Y   M   L   D   C   R    230
ACA GCT GGG AGT AAC AAC ACC CGT TTT GGC ATT GCT GCT AAG TAC ATG CTG GAT TGT AGA    690

 T   S   L   S   A   K   V   N   N   A   S   L   I   G   L   G   Y   T   Q   T    250
ACT TCT CTC TCT GCT AAA GTA AAT AAT GCC AGC CTG ATT GGA CTG GGT TAT ACT CAG ACC    750

 L   R   P   G   V   K   L   T   L   S   A   L   I   D   G   K   N   F   S   A    270
CTT CGA CCA GGA GTC AAA TTG ACT TTA TCA GCT TTA ATC GAT GGG AAG AAC TTC AGT GCA    810

 G   G   H   K   V   G   L   G   F   E   L   E   A   *                            283
GGA GGT CAC AAG GTT GGC TTG GGA TTT GAA CTG GAA GCT TAA TGTGGTTTGAGGAAAGCATCAGA    849

TTTGTCCCTGGAAGTGAAGAGAAATGAACCCACTATGTTTTGGCCTTAAAATTCTTCTGTGAAATTTCAAAAGTGTGAA

CTTTTTATTCTTCCAAAGAATTGTAATCCTCCCCACACTGAAGTCTAGGGGTTGCGAATCCCTCCTGAGGGAGACGCTT

GAAGGCATGCCTGGAAGTTGTCATGTTTGTGCCACGTTTCAGTTCAGTTCTGAAGTGTTATTAAATGTGTTCCTCAGCG
```

FIG.3B

ACAGTGTAGCGTCATGTTAGAGGAGACGATCTGACCCACCAGTTTGTACATCACGTCCTGCATGTCCCACACCATTTTT

TCATGACCTTGTAATATACTGGTCTCTGTGCTATAGTGGAATCTTTGGTTTTGCATCATAGTAAAATAAAATAAACCCA

TCACATTTGGAACATAAAAAAAAAAAAAAAAAAA

FIG.3C

```
 T   S   L   A   L   V   L   N   L   L   Q   I   Q   R   N   V   T   L   F   P     20
ACG AGC CTA GCC CTG GTG CTC AAC CTG CTG CAG ATC CAG AGG AAT GTC ACT CTC TTC CCC    60

 E   E   V   I   A   T   I   F   S   S   A   W   W   V   P   P   C   C   G   T     40
GAG GAG GTG ATC GCC ACC ATC TTT TCC TCC GCC TGG TGG GTC CCT CCC TGC TGC GGG ACA   120

 A   A   A   V   V   G   L   L   Y   P   C   I   D   S   H   L   G   E   P   H     60
GCA GCT GCT GTT GTT GGC CTA CTG TAC CCC TGT ATC GAC AGT CAC CTC GGA GAA CCC CAC   180

 K   F   K   R   E   W   A   S   V   M   R   C   I   A   V   F   V   G   I   N     80
AAA TTT AAG AGA GAA TGG GCC AGT GTC ATG CGC TGC ATA GCA GTT TTT GTT GGC ATT AAC   240

 H   A   S   A   K   L   D   F   A   N   N   V   Q   L   S   L   T   L   A   A    100
CAC GCC AGT GCT AAA TTG GAT TTT GCC AAT AAT GTC CAG CTG TCC TTG ACT TTA GCA GCC   300

 L   S   L   G   L   W   W   T   F   D   R   S   R   S   G   L   G   L   G   I    120
CTA TCT TTG GGC CTT TGG TGG ACA TTT GAT CGT TCC AGA AGT GGC CTT GGG CTG GGG ATC   360

 T   I   A   F   L   A   T   L   I   T   Q   F   L   V   Y   N   G   V   Y   Q    140
ACC ATA GCT TTT CTA GCT ACG CTG ATC ACG CAG TTT CTC GTG TAT AAT GGT GTC TAT CAG   420

 Y   T   S   P   D   F   L   Y   I   R   S   W   L   P   C   I   F   F   S   G    160
TAT ACA TCC CCA GAT TTC CTC TAT ATT CGT TCT TGG CTC CCT TGT ATA TTT TTC TCA GGA   480

 G   V   T   V   G   N   I   G   R   Q   L   A   M   G   V   P   E   K   P   H    180
GGC GTC ACG GTG GGG AAC ATA GGA CGA CAG TTA GCT ATG GGT GTT CCT GAA AAG CCC CAT   540
```

FIG.4A

```
 S   D   *                                                                182
AGT GAT TGA GTCTTCAAAACCACCGATTCTGAGAGCAAGGAAGATTTTGGAAGAAAATCTGACTGTGGATTATGAC  546

AAAGATTATCTTTTTTCTTAAGTAATCTATTTAGATCGGGCTGACTGTACAAATGACTCCTGGAAAAAACTCTTCACCT

AGTCTAGAATAGGGAGGTGGAGAATGATGACTTACCCTGAAGTCTTCCCTTGACTGCCCGCACTGGCGCCTGTCTGTGC

CCTGGAGCATTCTGCCCAGGCTACGTGGGTTCAGGCAGGTGGCAGCTTCCCAAGTATTCGATTTCATTCATGTGATTAA

AACAAGTTGCCATATTTCAAAAAAAAAAAAAAAAAMCTCGAGACCAACCCGCAGTTTTGTGTCAGTGCCCAAAGGAGGT

AGGTTGATGGTGCTTAACAAACATGAAGTATGGTGTAATAGGAATAATATTTATCCNAAAGATTTTTAAAAATAGGGCT

GTGTTTAAAAAAAAAAAAAAAAAA
```

FIG.4B

```
 M   C   H   S   R   S   C   H   P   T   M   T   I   L   Q   A   P   T   P   A      20
ATG TGT CAC TCT CGC AGC TGC CAC CCG ACC ATG ACC ATC CTG CAG GCC CCG ACC CCG GCC     60

 P   S   T   I   P   G   P   R   R   G   S   G   P   E   I   F   T   F   D   P      40
CCC TCC ACC ATC CCG GGA CCC CGG CGG GGC TCC GGT CCT GAG ATC TTC ACC TTC GAC CCT    120

 L   P   E   P   A   A   A   P   A   G   R   P   S   A   S   R   G   H   R   K      60
CTC CCG GAG CCC GCA GCG GCC CCT GCC GGG CGC CCC AGC GCC TCT CGC GGG CAC CGA AAG    180

 R   S   R   R   V   L   Y   P   R   V   V   R   R   Q   L   P   V   E   E   P      80
CGC AGC CGC AGG GTT CTC TAC CCT CGA GTG GTC CGG CGC CAG CTG CCA GTC GAG GAA CCG    240

 N   P   A   K   R   L   L   F   L   L   L   T   I   V   F   C   Q   I   L   M     100
AAC CCA GCC AAA AGG CTT CTC TTT CTG CTG CTC ACC ATC GTC TTC TGC CAG ATC CTG ATG    300

 A   E   E   G   V   P   A   P   L   P   P   E   D   A   P   N   A   A   S   L     120
GCT GAA GAG GGT GTG CCG GCG CCC CTG CCT CCA GAG GAC GCC CCT AAC GCC GCA TCC CTG    360

 A   P   T   P   V   S   P   V   L   E   P   F   N   L   T   S   E   P   S   D     140
GCG CCC ACC CCT GTG TCC CCC GTC CTC GAG CCC TTT AAT CTG ACT TCG GAG CCC TCG GAC    420

 Y   A   L   D   L   S   T   F   L   Q   Q   H   P   A   A   F   *                 157
TAC GCT CTG GAC CTC AGC ACT TTC CTC CAG CAA CAC CCG GCC GCC TTC TAA               471

CTGTGACTCCCCGCACTCCCCAAAAAGAATCCGAAAAACCACAAAGAAACACCAGGCGTACCTGGTGCGCGAGAGCGTA    550
```

FIG.5A

TCCCCAACTGGGACTTCCGAGGCAACTTGAACTCAGAACACTACAGCGGAGACGCCACCCGGTGCTTGAGGCGGGACCG 629

AGGCGCACAGAGACCGAGGCGCATAGAGACCGAGGCACAGCCCAGCTGGGGCTAGGCCCGGTGGGAAGGAGAGCGTCGT 708

TAATTTATTTCTTATTGCTCCTAATTAATATTTATATGTATTTATGTACGTCCTCCTAGGTGATGGAGATGTGTACGTA 787

ATATTTATTTTAACTTATGCAAGGGTGTGAGATGTTCCCTCTGCTGTAAATGCAGGTCTCTTGGTATTTATTGAGCTTT 866

GTGGGACTGGTGGAAGCAGGACACCTGGAACTGCGGCAAAGTAGGAGAAGAAATGGGGAGGACTCGGGTGGGGGAGGAC 945

GTCCCGGCTGGGATGAAGTCTGGTGGTGGGTCGTAAGTTTAGGAGGTGACTGCATCCTCCAGCATCTCAACTCCGTCTG 1024

TCTACTGTGTGAGACTTCGGCGGACCATTAGGAATGAGATCCGTGAGATCCTTCCATCTTCTTGAAGTCGCCTTTAGGG 1103

TGGCTGCGAGGTAGAGGGTTGGGGGTTGGTGGGCTGTCACGGAGCGACTGTCGAGATCGCCTAGTATGTTCTGTGAACA 1182

CAAATAAAATTGATTTACTGTCAAAAAAAAAAAAAAAAAACTCGAG 1228

FIG.5B

GAATTCGGCACGAGGMCAGGAGCTCCTTTWCTGCGTCTCCCATCATGGGGCTTAGGGTTGAGTCTTCA 68

GGTTCTGGGGGCAGGAAGGACGGGCACTCAGGAGGCCCCCTCCCCATCCACAGCCCCTCTTTGGGAGGGGGGAAACTTG 147

GCAACCCGGGAGGCATGTGGATCTTTTCCTAAGCAAGATGCTGAGCTGGAAAGATGGGGGTGTAAGGTAATGTCCCAAA 226

CTGAAACTTTGCCAGGCACTGGGAGAGGCTGTGAACTCTTTTCTGGCTTTAGAATTTAGGTCTAGATCCCAAAAGGCTA 305

AGTACCCCCTGGGGGCTAACCAGAGGCATGCCTGGGCTGAGCTGAACCTTCTGGTGCACTGGCCCCTGGCTGACTGCTC 384

TTCTGCAGGAAGTTGGAGGAGATTCCTGAAGTTGATTCCTCAGGCTGGATGTCCAAGGGGGTTGGAGTTTCTGATGTCT 463

TTCTGTCTCCCTCTCTTTTCTTTCTCTCCCTACCAGGTCCACTTCTTTCAGAGGGGCCTGCGGTGCTCTAAAAGTTCTC 542

CTGTTAAAGTTTAGAGCAAATTGGTTATTATTTTAAAATCAATAAAACTTTTAAAAGTACTAAGACAACTTCTAAGAGG 621

GGAGTGGACAGAGGGCCTGGTGGCAGCTCACAGTTTCTTTTCTGACCTTTGGTCTCACCCACCAAGTGTCCCACCTGAG 700

TGCCCACCTTGCCCACCTGAGGTAATGCCCTGGGGCTCCACCAGTCCAGATCCACAGGGCGCAGCCATGTGGGAGTGGC 779

GGCTGATTGTTACCCAGTAGTGTTGATAGCACATTATTCATAACAGCCAAGAGAGGAAGCAACCCAAATGTCCATTAG 858

CTGATAAATGGATAAATGAAATATGGTACGTCCGAAGAATGGAATATCATTCACCCTGAAAAAGAACGAAGTCCAGCA 937

CCAAAACGTGCTACAACATGGATGAACTTCGATGACTTTGTGCCACATGAAAGAAGAAGCCAGCCACAAAAGGCCATAT 1016

FIG.6A

```
                M   S   R   M   G   K   P   I   E   T   Q   K   S   P   P   P     16
ATTGTATGAAATGAA ATG TCC AGA ATG GGC AAA CCC ATA GAG ACA CAA AAA TCT CCG CCA CCT  1079

 P   Y   S   R   L   S   P   R   D   E   Y   K   P   L   D   L   S   D   S   T     36
CCC TAC TCT CGG CTG TCT CCT CGC GAC GAG TAC AAG CCA CTG GAT CTG TCC GAT TCC ACA  1139

 L   S   Y   T   E   T   E   A   T   N   S   L   I   T   A   P   G   E   F   S     56
TTG TCT TAC ACT GAA ACG GAG GCT ACC AAC TCC CTC ATC ACT GCT CCG GGT GAA TTC TCA  1199

 D   A   S   M   S   P   D   A   T   K   P   S   H   W   C   S   V   A   Y   W     76
GAC GCC AGC ATG TCT CCG GAC GCC ACC AAG CCG AGC CAC TGG TGC AGC GTG GCG TAC TGG  1259

 E   H   R   T   R   V   G   R   L   Y   A   V   Y   D   Q   A   V   S   I   F     96
GAG CAC CGG ACG CGC GTG GGC CGC CTC TAT GCG GTG TAC GAC CAG GCC GTC AGC ATC TTC  1319

 Y   D   L   P   Q   G   S   G   F   C   L   G   Q   L   N   L   E   Q   R   S    116
TAC GAC CTA CCT CAG GGC AGC GGC TTC TGC CTG GGC CAG CTC AAC CTG GAG CAG CGC AGC  1379

 E   S   V   R   R   T   R   S   K   I   G   F   G   I   L   L   S   K   E   P    136
GAG TCG GTG CGG CGA ACG CGC AGC AAG ATC GGC TTC GGC ATC CTG CTC AGC AAG GAG CCC  1439

 D   G   V   W   A   Y   N   R   G   E   H   P   I   F   V   N   S   P   T   L    156
GAC GGC GTG TGG GCC TAC AAC CGC GGC GAG CAC CCC ATC TTC GTC AAC TCC CCG ACG CTG  1499

 D   A   P   G   G   R   A   L   V   V   R   K   V   P   P   G   Y   S   I   K    176
GAC GCG CCC GGC GGC CGC GCC CTG GTC GTG CGC AAG GTG CCC CCC GGC TAC TCC ATC AAG  1559
```

FIG.6B

```
 V   F   D   F   E   R   S   G   L   Q   H   A   P   E   P   D   A   A   D   G    196
GTG TTC GAC TTC GAG CGC TCG GGC CTG CAG CAC GCG CCC GAG CCC GAC GCC GCC GAC GGC   1619

 P   Y   D   P   N   S   V   R   I   S   F   A   K   G   W   G   P   C   Y   S    216
CCC TAC GAC CCC AAC AGC GTC CGC ATC AGC TTC GCC AAG GGC TGG GGG CCC TGC TAC TCC   1679

 R   Q   F   I   T   S   C   P   C   W   L   E   I   L   L   N   N   P   R   •    236
CGG CAG TTC ATC ACC TCC TGC CCC TGC TGG CTG GAG ATC CTC CTC AAC AAC CCC AGA TAG   1739

TGGCGGCCCCGGCGGGAGGGGCGGGTGGGAGGCCGCGGCCACCGCCACCTGCCGGCCTCGAGAGGGGCCGATGCCCAGA  1818

GACACAGCCCCCACGGACAAAACCCCCCAGATATCATCTACCTAGATTTAATATAAAGTTTTATATATTATATGGAAAT  1897

ATATATTATACTTGTAATTATGGAGTCATTTTTACAATGTAATTATTTATGTATGGTGCAATGTGTGTATATGGACAAA  1976

ACAAGAAAGACGCACTTTGGCTTATAATTCTTTCAATACAGATATATTTTCTTTCTCTTCCTCCTTCCTCTTCCTTACT  2055

TTTTATATATATATATAAAGAAAATGATACAGCAGAGCTAGGTGGAAAAGCCTGGGTTTGGTGTATGGTTTTTGAGATA  2134

TTAATGCCCAGACAAAAAGCTAATACCAGTCACTCGATAATAAAGTATTCGCATTATAGTTTTTTTTAAACTGTCTTCT  2213

TTTTACAAAGAGGGGCAGGTAGGGCTTCAGCGGATTTCTGACCCATCSTGTACCTTGAAACTTGACCTCAGTTTTCAAG  2292

TTTTACTTTTATTGGATAAAGACAGAACAAATTGAAAAGGGAGGAAAGTCACATTTACTCTTAAGTAAACCAGAGAAAG  2371
```

FIG.6C

TTCTGTTGTTCCTTCCTGCCCATGGCTATGGGGTGTCCAGTGGATAGGGATGGCGGTGGGGAAAAGGAGAATACACTGG	2450
CCATTTATCCTGGACAAGCTCTTCCAGTCTGATGGAGGAGGTTCATGCCCTAGCCTAGAAAGGCCCAGGTCCATGACCC	2529
CCATCTTTGAGTTATGAGCAAGCTAAAAGAAGACACTATTTCTCACCATTTTGTGGAAATGGCCTGGGGAACAAAGACT	2608
GAAATGGGCCTTGAGCCCACCTGCTACCTTGCAGAGAACCATCTCGAGCCCCGTAGATCTTTTTAGGACCTCCACAGGC	2687
TATTTCCCACCCCCCAGCCAAAAATAGCTCAGAATCTGCCCATCCAGGGCTGTATTAATGATTTATGTAAAGGCAGATG	2766
GTTTATTTCTACTTTGTAAAAGGGAAAAGTTGAGGTTCTGGAAGGATAAATGATTTGCTCATGAGACAAAATCAAGGTT	2845
AGAAGTTACATGGAATTGTAGGACCAGAGCCATATCATTAGATCAGCTTTCTGAAGAATATTCTCMAAAAAAGAAAGTC	2924
TCCTTGGCCAGATAACTAAGAGGAATGTTTCATTGTATATCTTTTTTCTTGGAGATTTATATTAACATATTAAGTGCTC	3003
TGAGAAGTCCTGTGTATTATCTCTTGCTGCATAATAAATTATCCCCAAACTTAAAAAAAAAAAAAAAAAAAAAACTCGA	3082
G	3083

FIG.6D

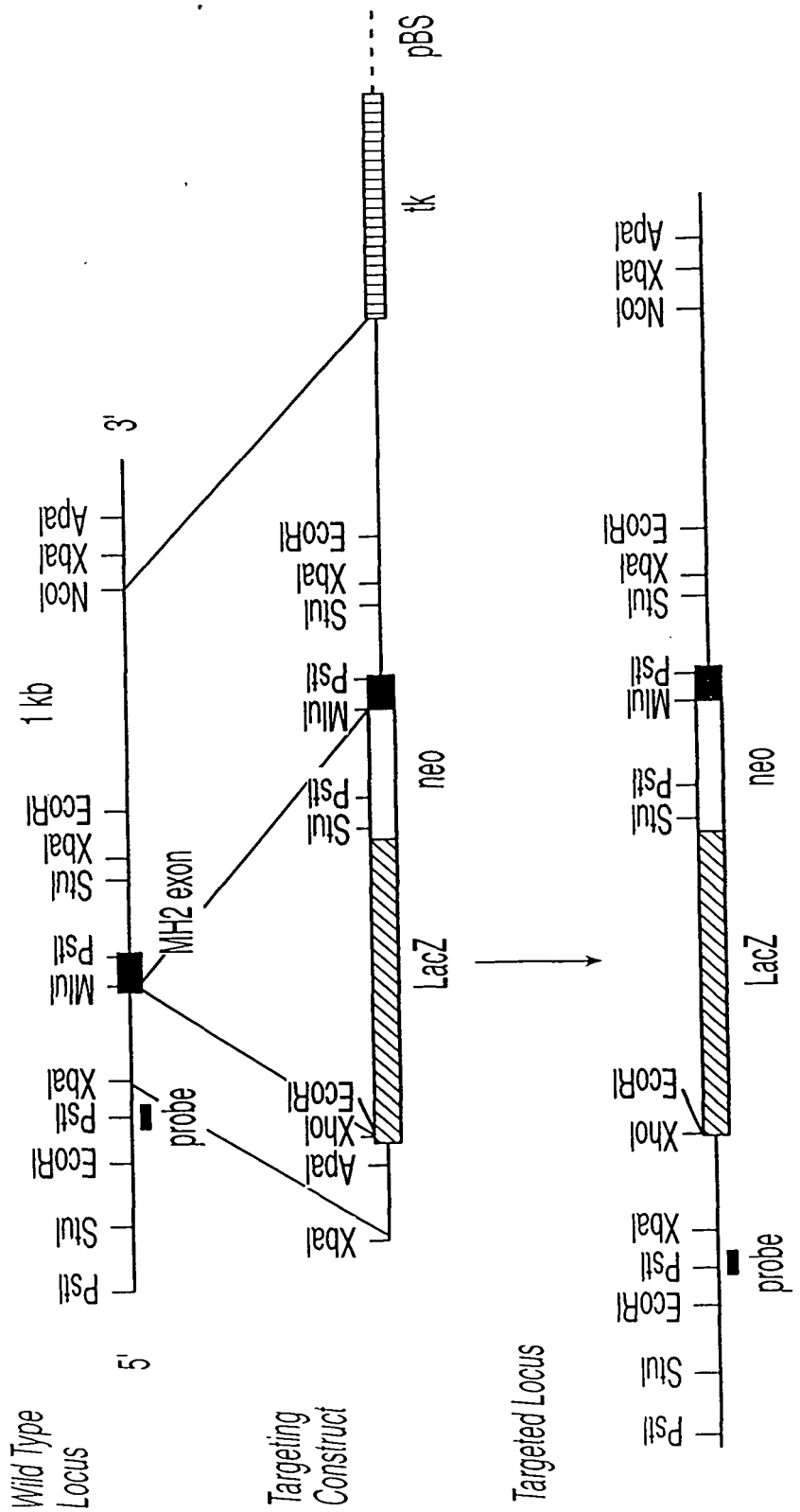

Wild Type Locus
5'
PstI
StuI
EcoRI
XbaI
PstI
probe
MluI
PstI
MH2 exon
StuI
EcoRI
XbaI
NcoI
1 kb
3'
ApaI
Targeting Construct
XbaI
ApaI
EcoRI
XhoI
StuI
PstI
MluI
PstI
StuI
neo
LacZ
tk
pBS
Targeted Locus
PstI
StuI
EcoRI
XbaI
PstI
probe
EcoRI
XhoI
LacZ
StuI
PstI
MluI
PstI
StuI
neo
EcoRI
XbaI
StuI
NcoI
XbaI
ApaI

FIG. 7A

FIG. 7B

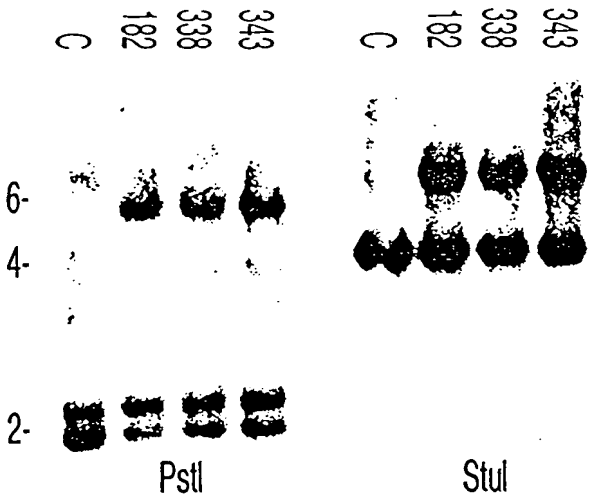


FIG. 7C

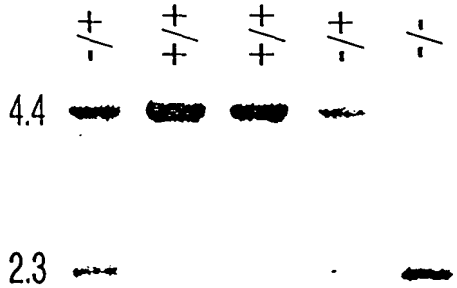
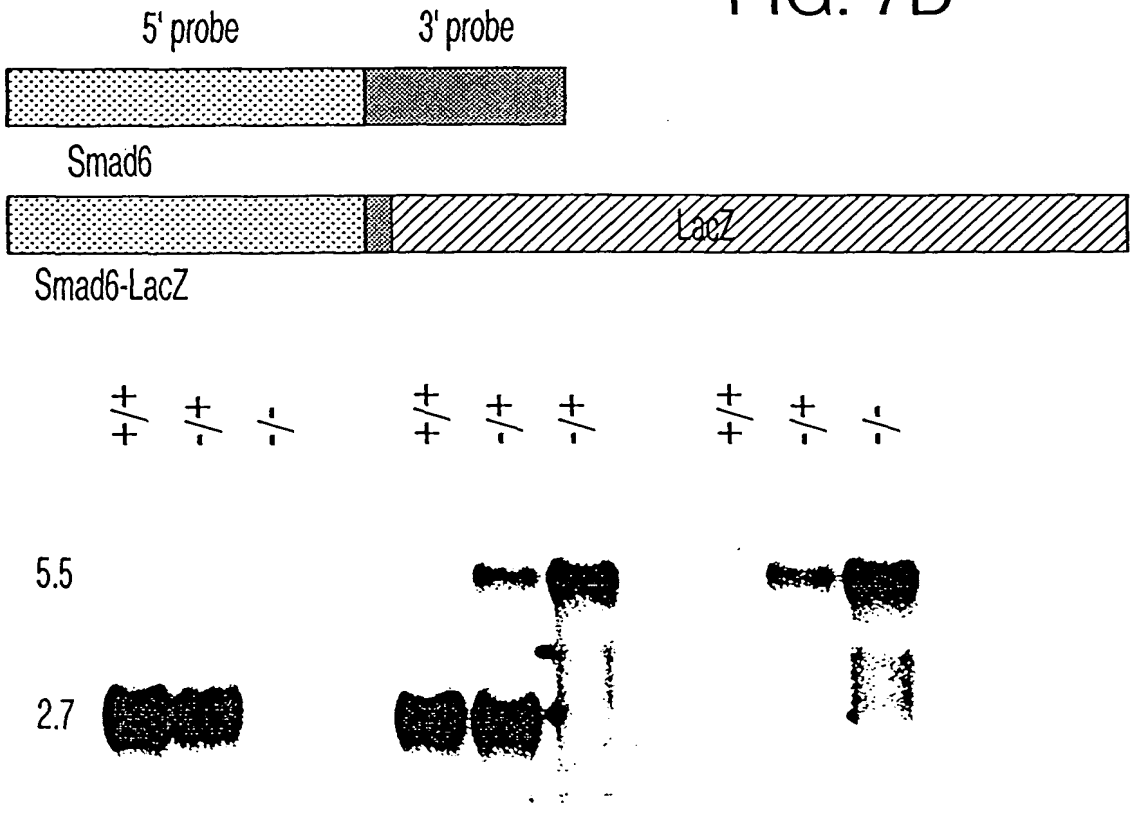


FIG. 7D



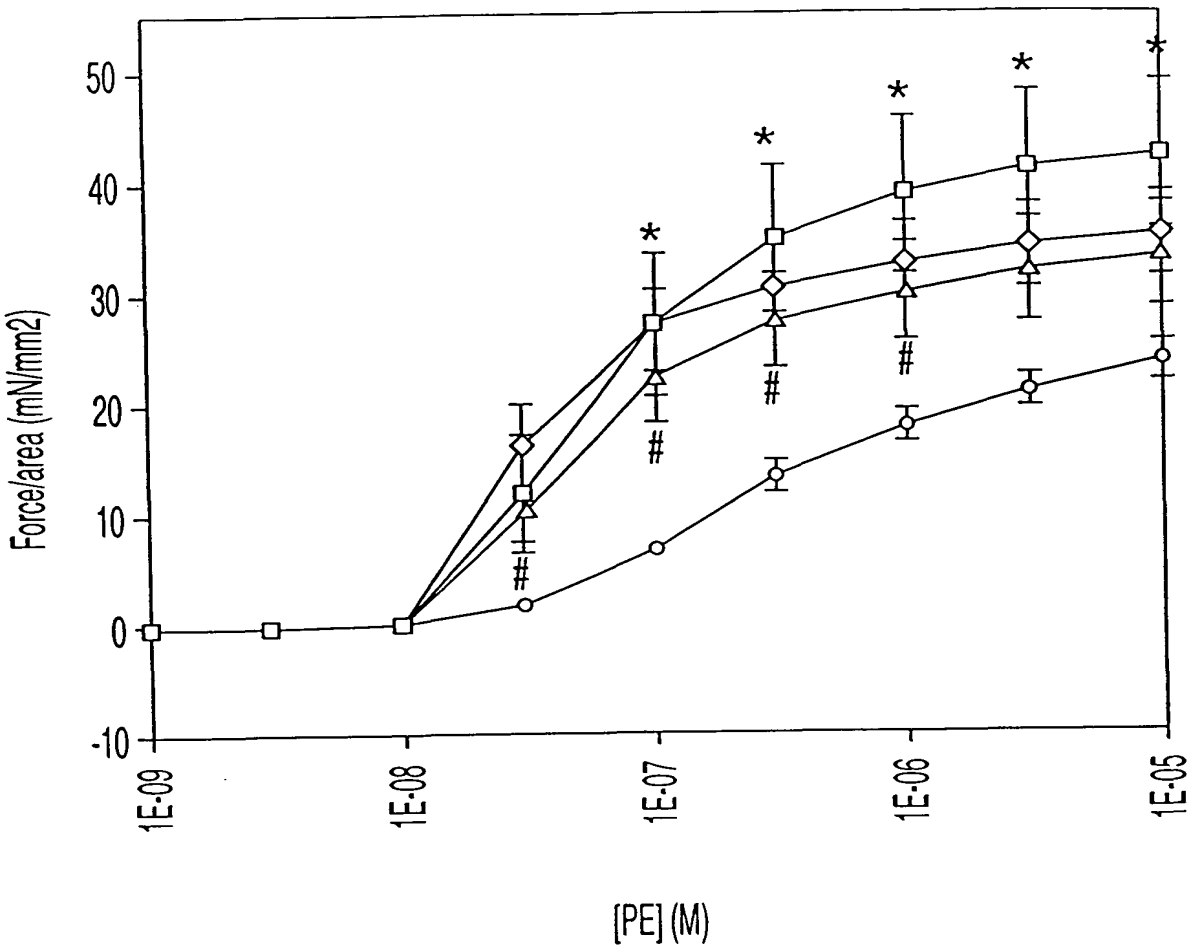


FIG. 8

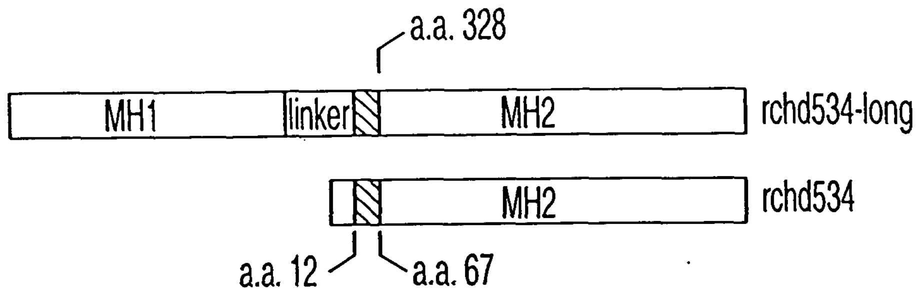


FIG. 9

```
ACGAGGACGACAGGCTGTGCGCGGTCTGCACGGCGCTCCGCGGCGGAGCTTCATGTGGGGCTGCGACCCGCGCAGCCGG 79

                                                                          M     1
CCCCTCGCTGAGGGAACGGACCCCCGGTAACCGGAGACCGCCTTCCCCCCCACCCCTGGCGCCAAAGGATATCGT ATG  157

 F   R   S   K   R   S   G   L   V   R   R   L   W   R   S   R   V   V   P   D    21
TTC AGG TCC AAA CGC TCG GGG CTG GTG CGG CGA CTT TGG CGA AGT CGT GTG GTC CCC GAC  217

 R   E   E   G   G   S   G   G   G   G   G   G   D   E   D   G   S   L   G   S    41
CGG GAG GAA GGC GCC AGC GGC GGC GGC GGT GGC GGC GAC GAG GAT GGG AGC TTG GGC AGC  277

 R   A   E   P   A   P   R   A   R   E   G   G   G   C   G   R   S   E   V   R    61
CGA GCT GAG CCG GCC CCG CGG GCA AGA GAG GGC GGA GGC TGC GGC CGC TCC GAA GTC CGC  337

 P   V   A   P   R   R   P   R   D   A   V   G   Q   R   G   A   Q   G   A   G    81
CCG GTA GCC CCG CGG CGG CCC CGG GAC GCA GTG GGA CAG CGA GGC GCC CAG GGC CCG GGG  397

 R   R   R   R   A   G   G   P   P   R   P   M   S   E   P   G   A   G   A   G   101
AGG CGC CGG CGC GCA GGG GGC CCC CCG AGG CCC ATG TCG GAG CCA GGG GCC GGC GCT GGG  457

 S   S   L   L   D   V   A   E   P   G   G   P   G   W   L   P   E   S   D   C   121
AGC TCC CTG CTG GAC GTG GCG GAG CCG GGA GGC CCG GGC TGG CTG CCC GAG AGT GAC TGC  517

 E   T   V   T   C   C   L   F   S   E   R   D   A   A   G   A   P   R   D   A   141
GAG ACG GTG ACC TGC TGT CTC TTT TCG GAG CGG GAC GCC GCC GGC GCG CCC CGG GAC GCC  577

 S   D   P   L   A   G   A   A   L   E   P   A   G   G   G   R   S   R   E   A   161
AGC GAC CCC CTG GCC GGG GCG GCC CTG GAG CCG GCG GGC GGC GGG CGG AGT CGC GAA GCG  637

 R   S   R   L   L   L   L   E   Q   E   L   K   T   V   T   Y   S   L   L   K   181
CGC TCG CGG CTG CTG CTG CTG GAG CAG GAA CTC AAA ACC GTC ACG TAC TCG CTG CTG AAG  697

 R   L   K   E   R   S   L   D   T   L   L   E   A   V   E   S   R   G   G   V   201
CGG CTC AAG GAG CGC TCG CTG GAC ACG CTG CTG GAG GCG GTG GAG TCC CGC GGC GGC GTG  757

 P   G   G   C   V   L   V   P   R   A   D   L   R   L   G   G   Q   P   A   P   221
CCG GGC GGC TGC GTG CTG GTG CCG CGC GCC GAC CTC CGC CTG GGC GGC CAG CCC GCG CCG  817

 P   Q   L   L   L   G   R   L   F   R   W   P   D   L   Q   H   A   V   E   L   241
CCG CAG CTG CTG CTC GGC CGC CTC TTT CGC TGG CCC GAC CTG CAG CAC GCC GTG GAG CTG  877

 K   P   L   C   G   C   H   S   F   A   A   A   A   D   G   P   T   V   C   C   261
AAG CCC CTG TGC GGC TGC CAC AGC TTC GCC GCC GCC GCC GAC GGC CCT ACC GTG TGC TGC  937

 N   P   Y   H   F   S   R   L   C   G   P   E   S   P   P   P   P   Y   S   R   281
AAC CCC TAC CAC TTC AGC CGG CTC TGC GGG CCC GAA TCT CCG CCA CCT CCC TAC TCT CGG  997

 L   S   P   R   D   E   Y   K   P   L   D   L   S   D   S   T   L   S   Y   T   301
CTG TCT CCT CGC GAC GAG TAC AAG CCA CTG GAT CTG TCC GAT TCC ACA TTG TCT TAC ACT 1057
```

FIG.10A

E T E A T N S L I T A P G E F S D A S M 321
GAA ACG GAG GCT ACC AAC TCC CTC ATC ACT GCT CCG GGT GAA TTC TCA GAC GCC AGC ATG 1117

S P D A T K P S H W C S V A Y W E H R T 341
TCT CCG GAC GCC ACC AAG CCG AGC CAC TGG TGC AGC GTG GCG TAC TGG GAG CAC CGG ACG 1177

R V G R L Y A V Y D Q A V S I F Y D L P 361
CGC GTG GGC CGC CTC TAT GCG GTG TAC GAC CAG GCC GTC AGC ATC TTC TAC GAC CTA CCT 1237

Q G S G F C L G Q L N L E Q R S E S V R 381
CAG GGC AGC GGC TTC TGC CTG GGC CAG CTC AAC CTG GAG CAG CGC AGC GAG TCG GTG CGG 1297

R T R S K I G F G I L L S K E P D G V W 401
CGA ACG CGC AGC AAG ATC GGC TTC GGC ATC CTG CTC AGC AAG GAG CCC GAC GGC GTG TGG 1357

A Y N R G E H P I F V N S P T L D A P G 421
GCC TAC AAC CGC GGC GAG CAC CCC ATC TTC GTC AAC TCC CCG ACG CTG GAC GCG CCC GGC 1417

G R A L V V R K V P P G Y S I K V F D F 441
GGC CGC GCC CTG GTC GTG CGC AAG GTG CCC CCC GGC TAC TCC ATC AAG GTG TTC GAC TTC 1477

E R S G L Q H A P E P D A A D G P Y D P 461
GAG CGC TCG GGC CTG CAG CAC GCG CCC GAG CCC GAC GCC GCC GAC GGC CCC TAC GAC CCC 1537

N S V R I S F A K G W G P C Y S R Q F I 481
AAC AGC GTC GCG ATC AGC TTC GCC AAG GGC TGG GGG CCC TGC TAC TCC CGG CAG TTC ATC 1597

T S C P C W L E I L L N N P R * 497
ACC TCC TGC CCC TGC TGG CTG GAG ATC CTC CTC AAC AAC CCC AGA TAG 1645

TGGCGGCCCCGGCGGGAGGGGCGGGTGGAGGCCGCGGCCACCGCCACCTGCCGGCCTCGAGAGGGGCCGATGCCCAGA 1724

GACACAGCCCCCACGGACAAAACCCCCCAGATATCATCTACCTAGATTTAATATAAAGTTTTATATATTATATGGAAAA 1803

AAAAAAAAAAAAAA 1817

FIG.10B